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Lipid Metabolism Pathway and Renal Tumor Therapy

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Abstract

Renal tumor remains as one of the common malignancy of the urinary system whose incidence and mortality is increasing over the years. Although the emergence of targeted drugs has greatly improved the prognosis of patients with advanced kidney cancer, the occurrence of drug resistance still brings huge treatment pressure to patients. Renal clear cell carcinoma (RCC), the most common pathological type of renal cancer, has been widely reported as a metabolic disease undergoing enormous metabolic reprogramming. This metabolic abnormality not only supports the synthesis of macromolecules such as proteins, lipids, and nucleic acids, but also promotes tumor progression. Changes in lipid metabolism, especially fatty acid metabolism, which is involved in the synthesis of biofilm components, provides energy for tumor progression, and regulates tumorigenesis. In this review, the key molecules of lipid metabolism pathway were systematically summarized, aiming to find potential therapeutic targets for RCC, and further elucidate the potential clinical application prospect of interfering with fatty acid metabolism pathway in the treatment of renal tumor.

Key words renal carcinoma, renal clear cell carcinoma, fatty acid metabolism, metabolic reprogramming, therapeutic targets

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Introduction

Renal cell carcinoma (RCC) is a common malignancy of the urinary system with an estimated 403,262 incidence, and 175,098 deaths from the disease worldwide [1]. Surgical resection is the first-line treatment for early-stage renal cancer, while for patients with advanced metastatic renal cancer, surgical treatment is less effective [2]. Although the emergence of targeted therapy has brought light to the treatment of advanced patients, the occurrence of drug resistance and adverse drug reactions has made the median survival rate less than 3 years [3]. Studies highlight renal cancer as a metabolic disease, and its occurrence and development involve many gene mutations, including Von Hippel-Lindau (VHL),and others [4]. The mutation of these genes directly changes the metabolic process of renal cancer cells. Changes in oxygen, energy and nutrient metabolism pathways play an important role in the occurrence and development of renal cancer [5].

Clear cell renal cell carcinoma (ccRCC) is a subtype of the most common form of RCC. ccRCC gets its name because of the "clear" state of its cytoplasm rich in lipids and glycogen pathological staining. Studies have shown that fatty acids (FAs) play an important role in the membrane structure, energy metabolism and signal transduction of ccRCC, suggesting that the regulation of fatty acid levels plays an important role in the regulation of tumor development, including the regulation of fatty acid synthesis, modification, and uptake from the microenvironment and release of fatty acids from other lipid species [6, 7]. Numerous studies have confirmed that fatty acid metabolism plays an important role in the progression of ccRCC, and targeting fatty acid metabolism may be a potential way to reverse drug resistance and improve its prognosis.

This article summarizes the research progress of key factors of fatty acid metabolism in ccRCC and expounds their role in the progression of ccRCC, so as to find potential therapeutic targets of ccRCC and further clarify the potential clinical application prospect of interfering with fatty acid metabolism pathway in the treatment of kidney tumors.

Lipid uptake

Induction of fatty acid uptake is a common way of cancer cell progression and treatment resistance. CD36, is a "scavenger" receptor that binds and internalize long chain fatty acids, low density lipoprotein and other substances, and has emerged as an important molecule that promote lipid uptake [8]. A joint metabolomic and genome-wide transcriptomic analysis showed that hypoxia-inducible factor (HIF-la) induce increased transcription of CD36 in early ccRCC and promote dietary fat uptake and storage. With the increase of ccRCC tumor stage, the transcription level of CD36 decreased, but the transcription level of fatty acid synthetase (FASN) increased. This suggests that advanced ccRCC tumors and metastatic ccRCC may compensate for the decreased ability to clear extracellular lipids by increasing lipid biosynthesis [9].

Fatty acid transport protein (FATP) is a group of proteins involved in fatty acid uptake, which is mainly located in cells or cell membranes and plays a key role in long-chain fatty acid transport. Studies have shown that tumor cells can increase intracellular lipid content by enhancing the expression of FATPs to promote cancer progression and treatment resistance [10]. FATPs consists of six isomers, which are encoded by specific genes and are tissue-specific [11]. FATP2 is a common subtype found in kidney tissue and plays an important role in regulating exogenous fatty acid transfer and intracellular maintenance of lipid homeostasis [12]. FATP4 is a protein encoded by SLC27A4 gene [13]. Studies have found that FATP4 is highly expressed in renal tumor tissues and is associated with poor prognosis of RCC [8]. Tumor cells can overexpress fatty acid binding protein (FABP), which is involved in intracellular and intracellular lipid transport, to promote tumor progression. One study revealed that FABPl expression decreased in ccRCC tissues, while FABP5, FABP6 and FABP7 expression increased in ccRCC tissues compared to paracancer tissues [14]. Higher expression levels of FABP5, FABP6 and FABP7 and lower expression levels of FABPl are associated with poor prognosis of ccRCC [15].

Lipid biosynthesis

FASN is a multienzyme protein complex and is an enzyme that can catalyze de novo synthesis of fatty acids. Multiple studies have reported that overexpression of FASN is closely related to the progression of multiple tumors such as breast cancer, and inhibition of FASN can inhibit the malignant phenotype of liver cancer cells [16]. In ccRCC, Choueiri et al. [17], found that FASN expression was negatively correlated with body mass index (BMI), and ccRCC patients with lower FASN expression had better overall survival rate. Ye et al. [18] confirmed that FASN expression positively correlated with ccRCC cell proliferation, migration, apoptosis and lipid drop formation, and regulated the metabolic disorders of ccRCC microenvironment.

ATP citrate lyase (ACLY) is a bridge between glucose metabolism and fatty acid synthesis and can catalyze the conversion of citric acid to acetyl-Coenzyme A(CoA), which directs excess glycolytic products to lipid synthesis, thus promoting tumor growth and differentiation. Studies have found that ACI and Y are highly expressed in ccRCC tissues, and the level of ACLY protein is positively correlated with the T stage and tumor grade of ccRCC [19].

Acetyl CoA carboxylase (ACC) is not only an enzyme that regulates fatty acid synthesis, but also participates in the oxidative metabolism of fatty acids [20]. ACC exists in cytoplasmic form (ACCA) and mitochondrial anchored form (ACCB), both of which catalyze acetyl CoA carboxylation to form malonyl CoA. ACCA is the main isomer mediating fatty acid synthesis, which can promote adipogenesis to meet the needs of cancer cells for rapid growth and proliferation. ACCB, an isoform near carnitine palmitoyl transferase 1 (CPT1), is a major regulator of CPT1 activity, and its expression and activity are inhibited in a variety of cancers [21].

Newly synthesized or over-consumed saturated fatty acids need to be saturated with stearyl CoA desaturase 1 (SCD1) in response to lipid toxicity and ER stress-induced apoptosis or iron death [21]. SCD1 is a regulatory enzyme that promotes lipid synthesis and plays an important role in cell membrane generation and signal transduction of cell metabolism. SCD1 is specifically highly expressed in ccRCC tumor tissues, and its expression level remains high throughout the progression of the disease [22].

Sterol regulatory element binding protein 1 (SREBP1) is a major regulator of fatty acid metabolism. SREBP1 is involved in the development of cancer and other diseases by regulating ACC, SCD1 and FASN transcription [23]. Yang et al. [24] found that lipid desaturation may be a metabolic marker of ccRCC, and demonstrated that SREBP1 is overexpressed in ccRCC cell lines and is necessary for lipid desaturation and cell growth in ccRCC. Zhang et al. [23] found that LINC01138 regulates the growth of ccRCC through SREBPI-mediated lipid desaturation and is associated with poor patient survival.

Lipid metabolism

The carnitine shuttle system is a key pathway in cancer metabolism and a key regulator of metabolites, providing energy and biosynthesis needs for malignant cells [24]. Over-expression

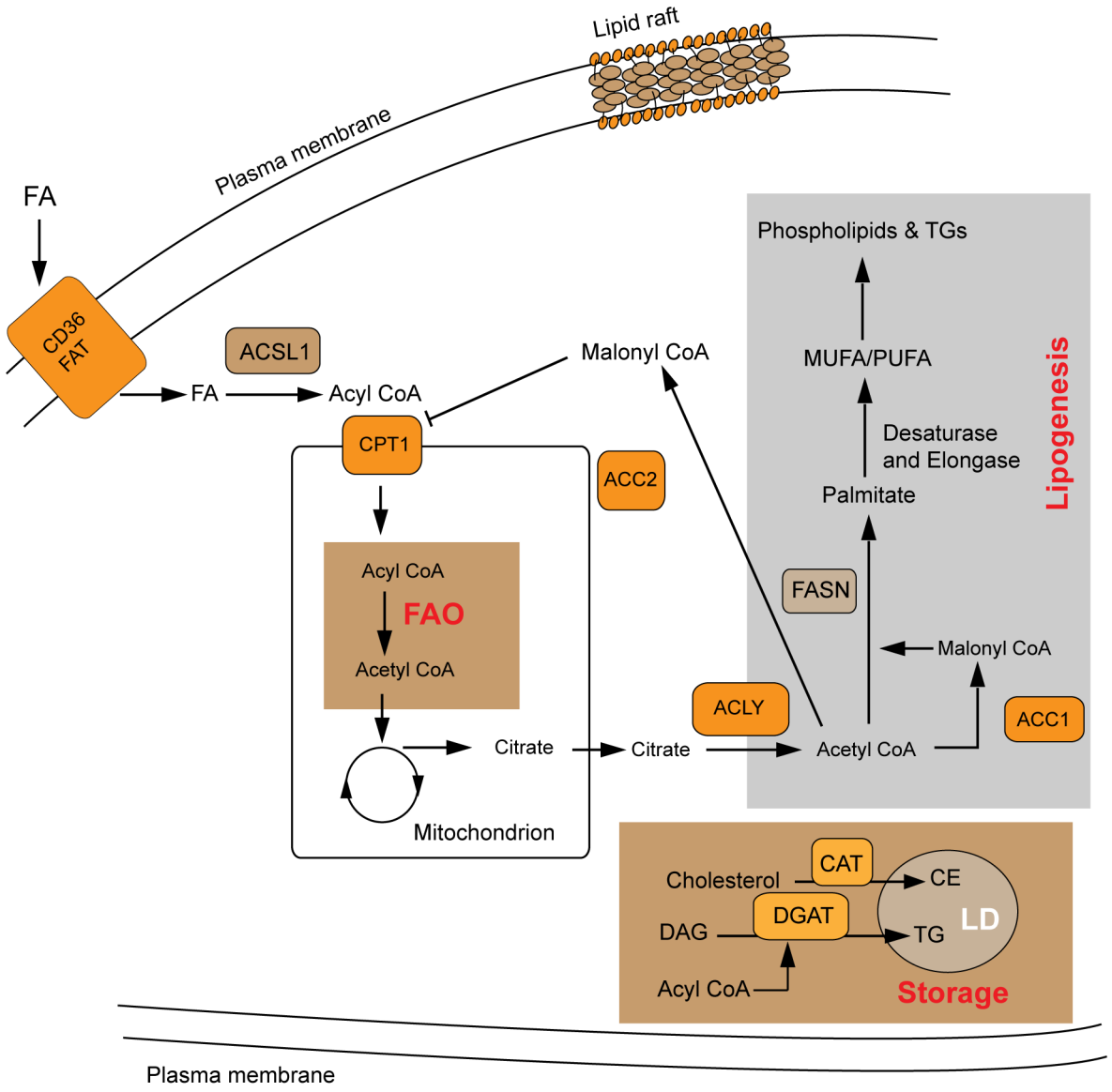

Figure 1. Lipid metabolism pathway mechanism. FAO: fatty acid oxidation; LDs: lipid droplets; FA: fatty acid; FAT: fatty acid translocase; DAG: diacylglycerol; CE: cholesterol ester; TG: triacylglycerol; ACSL1: Long-chain-fatty-acid-CoA ligase 1; ACC2: Acetyl CoA carboxylase 2; ACLY: ATP citrate lyase; FASN: fatty acid synthetase; ACC1: Acetyl CoA carboxylase 1; CPT1: carnitine palmitoyl transferase 1.

of carnitine palmitoyl transfeFase 1(CPT1) is associated with the progression of a variety of tumors, and multiple studies have shown that inhibition or silencing of CPT1 leads to apoptosis and cell proliferation of tumor cells. It is speculated that CPT1 can enable cell survival, not only by increasing fatty acid oxidation, but also by stimulating the activity of histone acetylase in the nucleus [25]. One study showed that CPT1, the rate-limiting enzyme of mitochondrial fatty acid transport, is the target gene of HIF and can participate in ccRCC.

The expression and activity of CPT1 in ccRCC are decreased relative to normal kidneys, which is associated with poor prognosis of patients. Mechanistically, CPT1 is inhibited by HIF1 and HIF2, reducing fatty acid transport to mitochondria and forcing fatty acids into lipid droplets for storage [26]. It has been found that after specific knockout of peroxisome proliferator activated receptor Y(PPARγ) in hepatocellular carcinoma, the expression of protease involved in de novo synthesis of fatty acids is significantly reduced [24]. By staining with oil red O and BODIPY493/503, Sanchez et al. [27] found that PPARY was indispensable for the viability, proliferation and migration of ccRCC cells in vivo and in vitro, but the knockout of PPAR7 would not affect the expression of FASN and SCD1 in ccRCC cell lines. Nor did PPAR7 significantly affect the content of glyceryl ester. Therefore, PPAR7 did not affect the "transparent" phenotype of ccRCC.

Figure 1 shows that lipid metabolism pathway mechanism.

The role of targeting fatty acid metabolic pathways in therapy

Extensive studies have shown that kidney cancer is a metabolism-related disease, and the occurrence of changes in lipid metabolism promotes tumor progression. Fatty acid metabolism, whether it provides energy substances, cellular components or signaling

molecules, can be regulated through a complex network of mechanisms to adapt to the metabolic needs of ccRCC progression. Metabolic changes in tumor microenvironment (TME) are also one of the important characteristics of ccRCC metastasis [28]. Therefore, reducing lipid levels in tumor cells and related cells in TME may affect tumor cell function in different ways. Thus, targeting lipid metabolism provides a new idea for the treatment of renal cancer. Fatty acids enter human tumor cells through passive diffusion or through lipid transporters such as CD36, FABPs and FATPs [29]. Targeting key molecules of fatty acid uptake pathway may be a new direction for tumor therapy and reversal of drug resistance. Studies have found that blocking CD36 by antibodies can prevent the uptake of lipids, thus inhibiting the metastasis of oral squamous cell carcinoma and colon cancer [30]. CD36-mediated reprogramming of lipid metabolism also promotes the resistance of breast cancer cells to HER-2 targeted therapy [31]. Targeting CD36 can reverse the decreased sensitivity of primitive CML cell subsets to imatinib [32]. Therefore, the combination of anticancer therapy with CD36 inhibitors may constitute a new therapeutic strategy to improve the efficiency of first-line drugs.

Fatty acids are first esterified into acyl CoA after entering the cell, and acyl CoA is transported to the mitochondria under the action of CPT1 to undergo fatty acid oxidation, which not only provides energy for tumor survival, but also provides reducing equivalent for tumor against oxidative stress. The uptake and metabolism of fatty acids are also regulated by the PPAR transcription factor family. Trastuzumab resistance has become a major obstacle in the treatment of HER-2 positive breast cancer patients. Studies have shown that AGAP2 ASl induced by mesenchymal stem cells can promote the stemness of breast cancer cells and induce trastuzumab resistance by upregulating CPT1 expression and inducing fatty acid oxidation [33]. Treatment of BRAF-mutated melanoma with MAPK inhibitors can result in significant tumor inhibition, but also lead to the prevalence of acquired drug resistance. Studies have found that PPARa-mediated CPTlA expression and increased fatty acid oxidation levels lead to MAPK inhibitor resistance in melanoma [34]. Thus, inhibitors targeting CPT1 or modulators of PPAR may be candidates for clinical treatment of cancer.

Citrate produced by tricarboxylic acid cycle is synthesized by ACLY, ACCs and FASN. Activated palmitate and other saturated fatty acids are desaturated by SCDs to produce monounsaturated fatty acids. Transcription of ACLY, ACCs, FASN and SCDs is also regulated by SREBP family [35]. ACLY and ACC are the rate-limiting enzymes of lipid synthesis, ACLY can divert excess glycolytic products to lipid synthesis. When selecting ACCl as a therapeutic target in breast cancer cells, attention should be paid to phosphorylation-mediated inactivation of ACCl, which can make breast cancer cells more aggressive and further induce tumor metastasis and recurrence by increasing the acetylation levels of intracellular acetylCoA and EMT-activating proteins [36]. In addition, some anti-obesity drugs are available, such as orlistat and other FASN inhibitors are also being tested in clinical trials in the hope of preventing tumor progression by inhibiting fatty acid synthesis [37, 38]. Orlistat has been shown to reduce angiogenesis and invasion in melanoma and to delay tumor growth in cisplatin-resistant ovarian cancer cells [39]. However, inhibition of FASN can compensatively cause CD36 up-regulation, and therefore, combined inhibition of FASN and CD36 may more favorably inhibit tumor progression [40]. SCD1 small molecule inhibitor A939572 can trigger the accumulation of saturated fatty acids, and in combination with tyrosine kinase or mTOR inhibitors can improve its efficiency and reduce its cytotoxicity [41]. Studies by Von Roemeling et al. [40] have shown that the combination of A939572 and tisirolimus can synergically inhibit the growth of ccRCC [22]. Wang et al. [42] found that SCD1 knockdown can inhibit the invasion of tumor cells, which may be caused by the reduced synthesis of fatty acids and the inhibition of Akt-mTOR signaling pathway. And subsequent studies found that interference with SCD1 combined with mTORCl/mTORC2 inhibitor AZDS055 in the treatment of ccRCC would produce more significant tumor inhibition effects. Kidney cancer cells, primary treated with A939572, proliferate more slowly than untreated cancer cells, and A939572 treated tumor cells had significantly higher mortality rates than untreated cancer cells after cisplatin treatment [43]. These results suggest that SCD1 inhibition significantly reduces cancer cell proliferation and increases cisplatin sensitivity, suggesting that this pathway may be related to ccRCC chemotherapy resistance. SREBPs is a major transcriptional regulator of adipogenesis. Its activation not only promotes the expression of lipid synthesis genes, but also promotes tumor progression and chemotherapy resistance. Therefore, in addition to being a prognostic marker, SREBPs can also be a potential therapeutic target for cancer treatment [44, 45].

Summary and Prospect

Fatty acids are regarded as important biochemical components in the development of cancer. These molecules are important components of cell membranes and organelles, recruiting signaling proteins in the form of "lipid rafts" and promoting protein-protein interactions in signal transduction. The composition and abundance of fatty acids can not only regulate membrane fluidity, but also change protein kinetic characteristics. For example, saturated Phospholipid (PL) has been shown to regulate signal transduction and be involved in cancer cell defense against oxidative damage and resistance to chemotherapy drug uptake [46]. In addition to their structural role, fatty acids coordinate signal transduction cascades and can also be broken down to biologically active components including sexual molecules that regulate a variety of carcinogenic processes [47].

Metabolic reprogramming is a hallmark of cancer and can play an important role in tumor progression by altering the metabolic capacity of tumor cells. Although most research on metabolic dysregulation in cancer has focused on carbohydrates, the importance of lipid metabolism-related alterations is beginning to be recognized. A large number of studies have confirmed that fat metabolism of tumor cells has an impact on biofilm synthesis, lipid synthesis and degradation, and signal transduction [48]. Abnormal fatty acid metabolism in RCC was first reported in 1987, and it was found by gas chromatography that cholesterol ester content in kidney tumor tissues was significantly higher than that in normal kidney tissues [49]. The reprogramming of fatty acid metabolism in RCC is mainly manifested in four aspects: (1) the role of de facto synthesis and exogenous uptake in cellular fatty acid pool; (2) the mechanism of molecular heterogeneity and carcinogenic signal transduction pathway regulating fatty acid metabolism; (3) Fatty acids as important mediators of cancer progression and metastasis reshape tumor microenvironment; therapeutic strategies targeting fatty acid metabolism in cancer [50].

In recent years, a variety of omics technologies, including proteomics, metabolomics and lipidomics, have made the research on ccRCC, a typical metabolic disease, enter a period of rapid development. Among them, the in-depth study on the mechanism of lipid metabolism in ccRCC is particularly eye-catching. As a metabolic disease characterized by classic molecular changes (VHL inactivation) and lipid deposition, ccRCC is an excellent model to study tumor lipid metabolism. Further study of the complex interaction between carcinogenic signaling pathways and dysregulation of fatty acid metabolism will provide broad prospects for revealing new metabolic pathways and improving targeted therapies.

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Ethical policy

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. Approval from institutional ethical committee was taken.

Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

WJW: Conception, design of study and manuscript preparation, literature search and review; CYX: Manuscript writting, Approval for the final version of the manuscript and funding supports.

Competing interests

The authors have no competing interest.

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